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Accuracy of on-site tests to detect asymptomatic bacteriuria in pregnancy: a systematic review and meta-analysis

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Cover letter

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London, 22 April 2016

Dr. Nancy C. Chescheir
Editor-in-Chief
Obstetrics & Genecology

Dear Dr. Chescheir

Re: "Accuracy of tests to detect asymptomatic bacteriuria during pregnancy: a systematic review and meta-analysis."

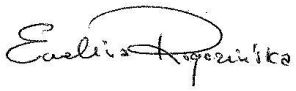
Undetected and untreated bacteriuria during pregnancy is associated with poor pregnancy outcomes such as preterm delivery or low birth weight of the infant. Women with the undetected infection have a 20- 30-fold increased risk of developing pyelonephritis compared to women without the condition.

Although some bodies recommend a routine urine culture screening in early pregnancy, it is an expensive, cumbersome, and time-consuming test that requires access to laboratory facilities.

Our systematic review is the first comprehensive and robust synthesis of accuracy data concerning on-site tests to detect asymptomatic bacteriuria during antenatal care. We have identified publications from 27 primary studies (combined number of 13,641 women) with test accuracy data for nine tests suitable for use in the asymptomatic population. More than half of the studies came from low to upper-middle income countries (17/27).

Our work was commissioned by the World Health Organization to inform the new guidelines for antenatal care aiming to identify evidence-based interventions and procedures to improve pregnancy outcomes. We strongly feel that the work is relevant to the scope of Obstetrics & Gynecology, and we will be grateful if you could consider our manuscript for publication in your journal.

Yours sincerely



Ewelina Rogozińska on behalf of the manuscript authors

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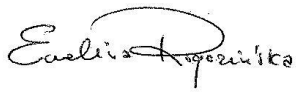
Friday, 22 April 2016

For the manuscript:

“Accuracy of on-site tests to detect asymptomatic bacteriuria in pregnancy: a systematic review and meta-analysis”

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.



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Accuracy of on-site tests to detect asymptomatic bacteriuria in pregnancy: a systematic review and meta-analysis

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Short Title: On-site tests for asymptomatic bacteriuria

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Conflict of interest: All authors have completed the Unified Competing Interest form an (available on request from the corresponding author) and declared that we have no conflicts of

interest. The views expressed are solely those of the authors and do not necessarily reflect the decisions or stated policy of the World Health Organization.

Precis: Sensitivity of the on-site tests to detect asymptomatic bacteriuria in pregnancy varies, however, their specificity to rule in the infection is high.

Abstract

Objective: The main objective of this systematic review of the literature was to determine the accuracy of on-site tests that require fewer resources to detect asymptomatic bacteriuria among pregnant women.

Data source: We searched the main electronic bibliographic databases from inception until June 2015 without language restrictions.

Methods of Study Selection: Two independent reviewers selected studies that recruited asymptomatic pregnant women to evaluate the accuracy of on-site tests in detecting the presence of bacteria in the urine using urine culture as a reference standard.

Tabulation, Integration, and Results: Data on women's characteristics, study design, sample collection, and handling were extracted along with to 2 x 2 tables, and synthesized, where possible, using a bivariate, hierarchical random effects model. Of 1,360 screened references, 27 papers (13,641 women) with test accuracy data on nine tests met the inclusion criteria. The most commonly evaluated test was urine dipstick. The pooled sensitivity and specificity of the dipstick to detect nitrites were 0.55 (95% CI 0.42 to 0.67) and 0.99 (95% CI 0.98 to 0.99), respectively. Griess test to detect nitrites had a sensitivity of 0.65 (95% CI 0.50 to 0.78) and specificity of 0.99 (95% CI 0.98 to 1·00). Dipslide with gram staining had a pooled sensitivity of 0.86 (95% CI 0.80 to 0.91) and specificity of 0.97 (95% CI 0.93 to 0.99).

Conclusions: The sensitivity of evaluated on-site tests to exclude bacterial urinary infection varies, however, their specificity to rule in disease is high.

Registration number: PROSPERO No. CRD42015027905

Keywords: test accuracy, asymptomatic bacteriuria, pregnancy, on-site test

Introduction

Asymptomatic bacteriuria, a common urinary tract infection, varies in prevalence by factors such as age, gender, level of sexual activity, etc. The prevalence of the infection in pregnancy ranges from 2–15% of whom 20–40% progress to symptomatic urinary infections (UTI).[1] Pregnant women with undetected asymptomatic bacteriuria are more likely to deliver prematurely[2] or low-birth-weight infants, and have a 20- 30-fold increased risk of developing pyelonephritis compared with those without the infection.[3]

Although some bodies recommend a routine urine culture screening in early pregnancy[4, 5], it is an expensive, cumbersome, and time-consuming test (taking 24 to 48 hours to obtain results) that requires access to laboratory facilities. There is a wide range of tests requiring fewer resources and minimal training,[6] of which the most commonly used to detect the presence of bacteria instantly in the urine is a dipstick. Available evidence synthesis on their accuracy in pregnancy is limited in range of evaluated test[7], and methodological strength.[6, 8]

We bridge the above gap through a systematic and comprehensive evaluation of a wide range of on-site tests used to detect bacteriuria compared against urine culture as a reference standard in asymptomatic pregnant women taking into account potential sources of heterogeneity.

Methods

The review was conducted prospectively guided by a pre-defined protocol (PROSPERO No. CRD42015027905). We followed current standards of evidence synthesis for test accuracy[9-11] and reported findings in compliance with guidelines.[12]

Sources

We searched major databases such as Medline, Embase, Web of Science, Scopus, and a specialized database of Latin-American literature (LILACS) for studies published from database inception to August 2014, with no language restrictions. The search was updated to June 2015. The search strategy combined terms such as: 'Pregnancy', 'Antenatal', 'Gestation', 'asymptomatic bacteriuria' and 'Urinary Tract Infections' and applied a filter for test accuracy studies (for details see Appendix 1).[13]

Study selection

Two independent reviewers (ER and SF) screened references and full-text of previously selected articles. The consensus on the eligibility of evaluated publications was reached through discussion, or consultation with a third reviewer (KSK). We looked for studies reporting the accuracy of any on-site tests to detect asymptomatic bacteriuria among pregnant women without symptoms of urinary tract infections or not on antibiotic treatment. The reference standard had to be a urine culture, and asymptomatic bacteriuria had to be defined as equal, or more than 10^5 Colony Forming Units of a single organism per mL of urine.[8] Test accuracy had to be reported in a way allowing construction of 2 x 2 tables. We excluded studies with a case-control design and were reference standard was not reported or used a different definition of bacteriuria than specified above as this design and variation in reference standard were associated with bias.[14]

Data were extracted independently by ER and SF on to a piloted sheet. We collected authors' details, year of publication, country, women's characteristics, gestational age at testing; urine collection method, storage, and handling. The data were tabulated, crossed checked and in the case of discrepancies discussed between the reviewers. The studies were grouped according to country income (low-, low-middle, upper-middle) using the World Bank classification.[15] The

risk of bias and applicability of included studies were assessed by two independent reviewers (ER and SF) using the QUADAS-2 tool[10] tailored for this review. Study quality was assessed for selection of participants, implementation of the index test and the reference standard, and patient flow. Studies with low risk of bias used a suitable spectrum of participants, recruited in consecutive or random manner; all participants were tested using the same reference standard, and the majority of the study population was included in analyses. Any disagreements over quality assessment were resolved by a third reviewer (KSK). We did not assess publication bias due to limitations of available methods.[16, 17]

We calculated test accuracy estimates (sensitivity, specificity, and likelihood ratios for positive and negative test result) with 95% confidence intervals (CIs). Heterogeneity was investigated visually on forest plots with sensitivity and specificity estimates (with 95% confidence intervals) for individual studies. The impact of quality of study design, the reliability of population description, and sample collection and storage was explored through sensitivity analyses. All analyses were conducted using STATA version 12.1.[18] If less than required number of data points was available, we pooled accuracy of sensitivity and specificity, and likelihood ratios using univariate model using *metaprop* and *metan* commands, respectively. Where a higher number of studies was available, we pooled the accuracy parameters using bivariate, random effects model as implemented in *metandi*[19] and *midas*[20] commands . Posttest probabilities were calculated using following formula: O= p1/(1 - p1), p2 = O * L, p = p2 /(1 + p2), where p1 pretest probability, O pretest odds, p2 posttest odds, L likelihood ratio, p posttest probability.[21]

Results

Out of the 1,360 references, 39 examining 27 types of index tests appeared initially to meet the inclusion criteria (Figure 1). After exclusion of tests not suitable for use in the asymptomatic population, we were left with 27 studies with nine index tests. List of all identified tests and reasons for study exclusion can be found in Appendix 2. Selected tests were: dipstick with only nitrites marker as positive, dipstick with nitrites or leucocytes as positive, urine analysis with bacteria count, dipslide with gram stain, Uricult (Orion Diagnostica, Espoo, Finland), Microstix-3 (Bayer Schering Pharma, Berlin, Germany), Griess test to detect nitrites, chlorhexidine reaction, and uriscreen catalase test. Reference of the included studies can be accessed in Appendix 3.

The majority of identified studies were conducted in low-middle (11 studies) or upper-middle (five studies) income countries; ten in high-income countries and only one in a low-income country. The studies were published between 1981 and 2015; ten studies were published before the year 2000, nine between 2000 and 2010 and remaining eight in the last five years. The majority (19/27) of included studies contributed to evidence synthesis accuracy data of only one test (Table 1) with urine dipstick as the most commonly reported test. Urine was mostly collected through clean catch midstream technique and as a random voided or first-morning sample in 56% of studies (15/27). Use of sterile containers was mentioned in ten out of 27 studies. More details on urine sample collection, handling and storage, and the details of urine culture incubation can be found in Appendix 4.

The overall quality of included studies was moderate (Figure 2). Twelve out of 27 studies gave a proper description of patients' selection with the remaining not giving enough details to assess this methodological aspect of the study. There was no concern for risk of bias due to index test implementation in over 80% of the studies (22/27). Similarly, for the reference

standard except two studies, the performance of the urine culture was classified as high risk of bias. Flow and timing were described with sufficient details in one-third of studies (9/27). The high concern over the applicability of findings was due to the type of the reference standard in five studies and the index test in one case. The main concern in the case of the reference standard was the use of a double urine culture to confirm the diagnosis of bacterial infection.

Twenty-one studies (9,491 women) reported accuracy data for the detection of nitrites using urine dipstick and eight for the combination of positive nitrites or leukocytes (5,940 women). The average prevalence of asymptomatic bacteriuria in these studies were 0.08 (95% CI 0.06 to 0.10). The pooled sensitivity of urine dipstick for positive nitrites in detecting infection was 0.55 (95% CI 0.42 to 0.67) with specificity 0.99 (95% CI 0.98 to 0.99). The pooled sensitivity of positive nitrites or leukocytes was 0.73 (95% CI 0.59 to 0.83) with specificity 0.89 (95% CI 0.79 to 0.94). For both tests, the accuracy parameters were heterogeneous with greater variability in sensitivity than specificity (Figure 3), 95% prediction contour was visibly wider for the combined markers (Appendix 5). The likelihood ratio of the positive test result for the urine dipstick test using only nitrites marker was 54.1 (95% CI 26.5 to 266.21.

One study each contributed data on the specificity and sensitivity of chlorhexidine reaction and uriscreen catalase tests. The sensitivity of the former was 1.00 (95% 0.65 to 1.00) and specificity (0.54, 95% CI 0.46 to 0.62) (Table 2). Use of Griess test to detect the presence of nitrites was reported in two studies (728 women). The sensitivity of the test was comparable to Uriscreen catalase test 0.65 (95% CI 0.50 to 0.78) with a specificity of 0.99 (95% CI 0.98 to 1.00). The likelihood of the positive test result was 56·6 (95% CI 12.6 to 255.1). Only one study reported the accuracy of the microscopic technique with the bacterial count in a centrifuged urine sample with a clearly defined threshold of more than 20 bacteria per High

Power Field (HPF). The sensitivity and specificity were 0.78 (95% CI 0.45 to 0.94) and 0.92 (95% CI 0.88 to 0.94), respectively.

Accuracy data of three dipslide-based tests included evaluation of Uricult (two studies), Microstix-3 (one study) and a generic dipslide method with gram stain dyeing and threshold of one or more bacteria per Oil Immersed Field (OIF) (six studies). Uricult had a sensitivity of 0.92 (95% CI 0.69 to 1.00) and specificity 0.85 (95% CI 0.24 to 1.00). The dipslide with gram staining on uncentrifuged urine had sensitivity and specificity of 0.86 (95% CI 0.80 to 0.91) and 0.97 (95% CI 0.93 to 0.99) respectively (Figure 3). The likelihood ratio of the positive test result was 30.2 (95% CI 11.9 to 76.6).

Sensitivity analysis was possible for dipstick with nitrites only as a marker, dipstick with nitrites or leukocytes and dipslide with gram staining. In all three cases, we explored the impact of population description and use of the sterile containers for urine storage. Neither of the factors changed the summary accuracy of the dipslide with gram staining. Analysis limited to studies with a clearly described population (asymptomatic women or not taking antibiotics) showed a marginal reduction in sensitivity (by 4%) for urine dipstick with positive leukocyte or nitrites marker. The pooled sensitivity of urine dipstick (nitrites with or without leukocytes) limited to studies providing details of urine container's sterility, presented a minimal increase in parameter precision. Findings from studies with low risk of bias and studies where the type of urine sample was not properly described had a minimal impact on the sensitivity the dipstick test with no change in the value of the pooled specificity.

Discussion

Out of 27 types of index tests identified in the literature, nine were suitable for use in the asymptomatic population. Three of them (urine dipstick, Griess test and dipslide with gram staining) had values of likelihood ratios for positive test result indicative of their usefulness (values > 10) in detecting asymptomatic bacteriuria during antenatal care. All test were minor to moderate usefulness to rule out the infection (likelihood ratios for negative result between 0.5–0.1).

This systematic review is the first comprehensive and robust synthesis of accuracy data concerning on-site tests to detect asymptomatic bacteriuria during antenatal care. Prospectively registered protocol with pre-specified population, reference standard, and definition of the outcome informed study selection, data extraction and analysis. On all stages of the review process, we followed current guidelines and standards.[11] The literature search in electronic databases restricted to test accuracy studies due to pragmatic reasons was supplemented by manual reference check. The publication bias due to limitations of available statistical methods[16, 17] was not investigated in this review, however, we did undertake an extensive exploration of the heterogeneity between estimates of tests accuracy in individual studies.

The main limitation of this review was poor reporting in individual studies and paucity of data. The quality assessment was hindered by insufficient reporting of characteristics or recruited women, their flow through the study and timing between the use of index test and reference standard. Empirical evidence showed that test accuracy estimates can be affected by flaws in study design and its conduct.[14] The estimates of test accuracy for four included tests were based on data from single studies with small sample sizes.[22-24] This makes the parameters less reliable (wide confidence intervals) and more prone to chance findings. In order to compare the accuracy of all identified tests, we used the univariate model to pool sensitivity and specificity

estimates when less than four studies were available. Even though this approach does not account for correlation between two parameters as in the bivariate model, the findings should be fairly similar.[25] Despite these limitations our findings merit consideration as the most robust and current evidence synthesis.

The prevalence of asymptomatic bacteriuria in included studies ranged from 2 – 23% which overlaps with previously reported range[1]. The likelihood ratios of the positive test result for the urine dipstick test (only nitrites), Griess test and generic dip slide with gram staining (bacterial count > 1/OIF) were indicative of tests usefulness in ruling in asymptomatic bacteriuria.[21] The likelihood ratio of positive result with Dipslide Uricult due to wide confidence intervals cannot be considered reliable. However, its likelihood ratio for the negative result was the only one indicative its usefulness to rule out the infection (< 0.1). Likelihood ratios can be used to help adapt the results of the findings to individual situation basing on Bayes' theorem.[26] With pretest probability derived from identified studies we calculate the posttest probability of having the infection with a positive and negative test result (Table 2). Two out of nine evaluated tests (urine dipstick with positive nitrites and Griess test) increased the probability from 8·0% to above 80.0% in case of positive result, and both reduced it by half in case of a negative result. Need for training and access to basic laboratory facilities might make Griess test and Gram staining less attractive than urine dipstick in resource-limited settings.

Undetected and subsequently not treated asymptomatic bacteriuria is linked to pyelonephritis and other complications.[3] Antibiotic treatment seem to reduce the risk of pyelonephritis in pregnancy and undesired pregnancy outcomes (preterm birth and low birth weight). Women incorrectly classified as positive (false positive) may be exposed to an unnecessary course of antibiotics with not well documented adverse effects.[27] In light of lack of robust evaluation of

harms and increasing antimicrobial resistance, it is crucial to correctly identify women who will truly benefit from the treatment.[8]

All identified on-site tests when positive increased posttest probability of detecting asymptomatic bacteriuria during the antenatal period. Urine dipstick, Griess test and dipslide with gram staining are most useful point-of-care options for ruling in the infection. Future research should aim to support the clinical decision-making on the management of asymptomatic pregnant women when access to urine culture is limited.

Contributors

ER selected eligible texts, data extraction form, extracted data, wrote the protocol, cleaned and analyzed the data, drafted and revised the manuscript. SF selected eligible texts, extracted data, and revised the paper. KSK, LM resolved discrepancies between reviewers and revised the draft paper. ER did statistical analysis, supervised by JZ. All authors contributed to the drafts and final version of the manuscript.

ER have full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Figures

Figure 1 Flow diagram describing selection of studies and tests

Figure 2 Study quality assessment using QUADAS-2 tool

Figure 3 Overview of sensitivity and specificity of tests to detect asymptomatic bacteriuria in pregnancy

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Ewelina Rogozinska

Table 1 Characteristics of studies evaluating accuracy of on-site tests to detect asymptomatic bacteriuria in antenatal care settings

Study ID	Publication Year	Country	Number of women	Prevalence of the infection (95% CI)	Index test(s)
Abbasi 1985[1]	1985	USA	65	0.05 (0.02–0.13)	Dipstick
Anandkumar 2011[2]	2011	India	300	0.13 (0.09–0.17)	Dipslide with gram staining
Archbald 1984[3]	1984	USA	287	0.03 (0.02–0.06)	Dipstick, Urinalysis (bacteria count), Dipslide (Microstix–3)
Awonuga 2011[4]	2011	Nigeria	205	0.11 (0.07–0.16)	Dipstick
Bachman 1993[5]	1993	USA	1047	0.02 (0.02–0.03)	Dipstick, Dipslide with gram staining
Balamurugan 2012[6]	2012	India	100	0.13 (0.08–0.21)	Dipstick
Campos-Outcalt 1985[7]	1993	USA	299	0.05 (0.03–0.08)	Dipstick
Demilie 2014[8]	2014	Ethiopia	330	0.08 (0.06–0.12)	Dipstick
Eigbefoh 2008[9]	2008	Nigeria	400	0.22 (0.18–0.26)	Dipstick
Gayathree 2010[10]	2010	India	900	0.07 (0.05–0.09)	Dipstick, Dipslide with gram staining
Graninger 1992[11]	1992	Germany	1000	0.13 (0.11–0.15)	Dipstick
Greeff 2002[12]	2002	South Africa	247	0.23 (0.19–0.29)	Dipslide (Uricult)
Jayalakshmi 2008[13]	2008	India	630	0.07 (0.06–0.10)	Dipstick, Dipslide with gram staining

Kacmaz 2006[14]	2006	Turkey	250	0.04 (0.02–0.07)	Dipstick
Khattak 2004[15]	2004	Pakistan	290	0.06 (0.04–0.10)	Griess test
Kovavisarach 2008[16]	2008	Thailand	360	0.10 (0.07–0.14)	Dipstick
Mathews 1998[17]	1998	India	438	0.07 (0.05–0.10)	Griess test
Mignini 2009[18]	2009	Argentina	2353	0.14 (0.13–0.16)	Dipstick, Dipslide (Uricult)
Mukherjee 2015[19]	2015	India	250	0.08 (0.06–0.12)	Dipstick, Dipslide with gram staining
Okusanya 2014[20]	2014	Nigeria	150	0.05 (0.02–0.09)	Dipstick, Chlorhexidine reaction
Pallarés 1990[21]	1990	Spain	74	0.12 (0.07–0.22)	Dipstick, Dipslide with gram staining
Plauche 1981[22]	1981	USA	561	0.13 (0.09–0.18)	Dipstick
Shelton 2001[23]	2001	USA	200	0.10 (0.07–0.15)	Dipstick
Soisson 1985[24]	1985	USA	1062	0.06 (0.05–0.07)	Dipstick
Teppa 2005[25]	2005	Venezuela	150	0.19 (0.13–0.26)	Uriscreen catalase test
Tincello 1998[26]	1998	UK	893	0.05 (0.04–0.07)	Dipstick
Titoria 2014[27]	2014	India	800	0.05 (0.04–0.07)	Dipstick

3 References of the included studies are available in *Appendix*

Table 1 Likelihood ratios and post-test probabilities for tests–detect asymptomatic bacteriuria in antenatal care settings

Index test	Likelihood ratio for a positive result (95% CI)	Probability* of infection after positive testing (%)	Likelihood ratio for a negative result (95% CI)	Probability* of infection after negative testing (%)
Dipstick: Nitrites positive	**54.08** (26.50–266.21)	82.5	0.46 (0.35–0.61)	3.9
Dipstick: Leucocytes or nitrites positive	6.36 (3.31–12.21)	35.6	0.31 (0.19–0.49)	2.6
Chlorhexidine reaction	2.03 (1.58–2.61)	15.0	0.12 (0.01–1.71)	1.0
Uriscreen catalase test	5.69 (3.15–10.32)	33.1	0.44 (0.27–0.70)	3.7
Griess test (nitrites)	**56.62** (12.57– 255.06)	83.1	0.36 (0.25–0.53)	3.0
Urinalysis (bacteria count >20/HPF)	9.4 (5.56–15.89)	44.9	0.24 (0.07–0.82)	2.1
Dipslide with gram staining (bacteria count ≥1/OIF)	**30.22** (11.91–76.64)	72.4	0.14 (0.09–0.21)	1.2
Dipslide (Uricult)	20.04 (0.01–5.2e+04)	63.5	0.09 (0.00–2.16)	0.8
Dipslide (Microstix-3)	9.07 (5.21–15.77)	44.1	0.36 (0.18–0.74)	3.0

**Pretest probability of 8.0% was a median prevalence derived from included studies*

Figure 1 Study selection

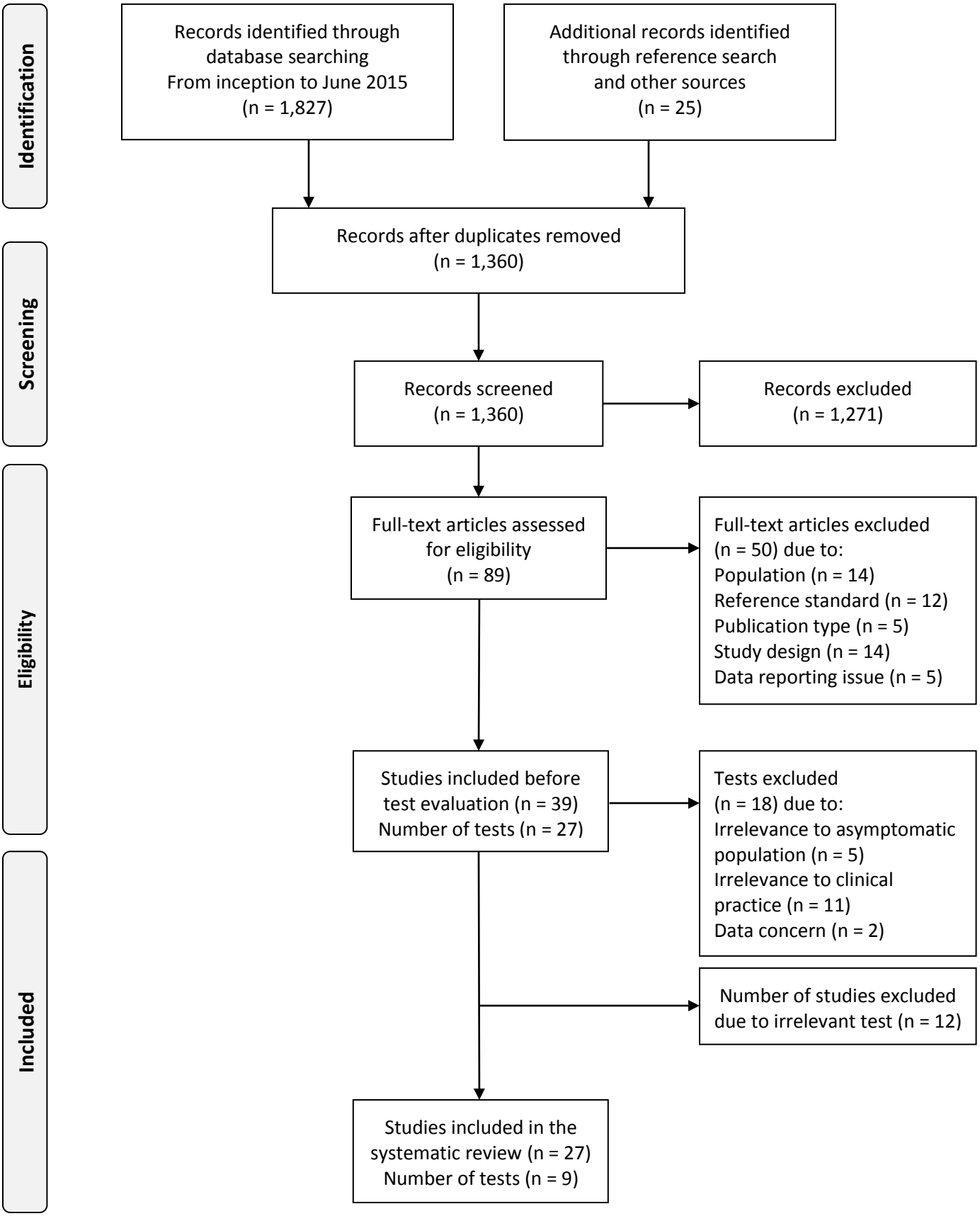
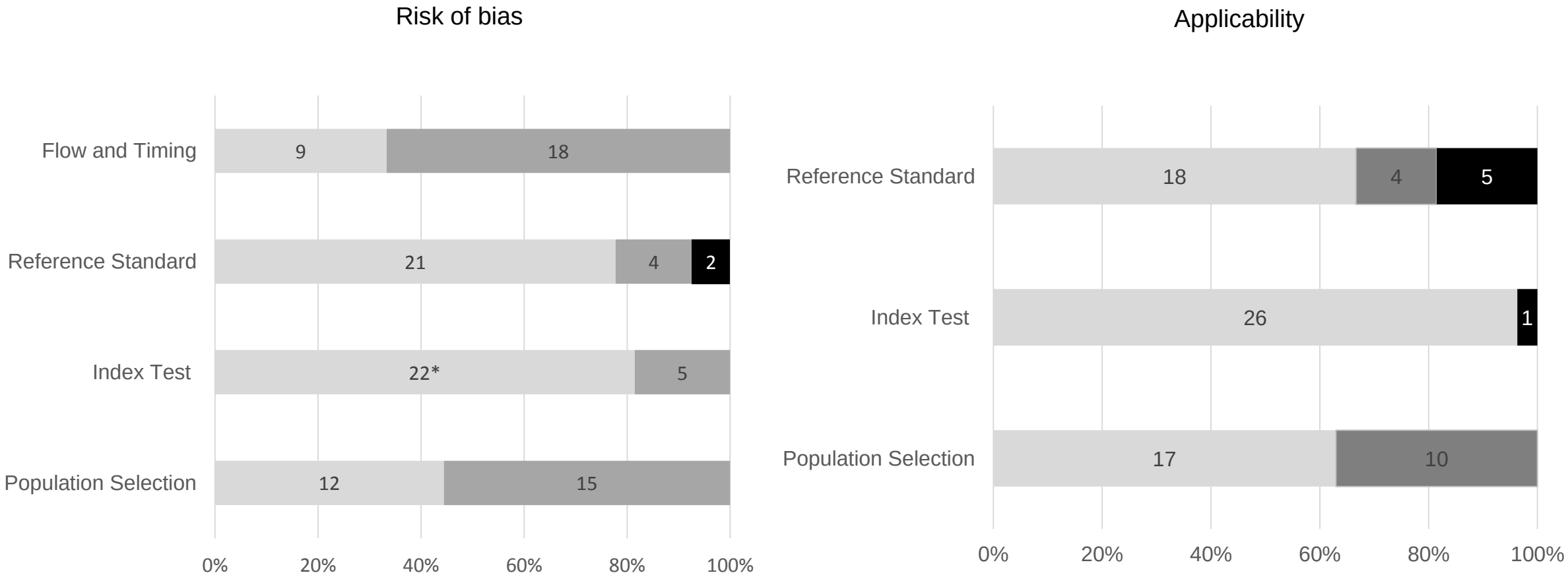


Figure 1 Flow diagram describing studies and tests selection stages

Figure 2 Quality assessment



**For Okusanya 2014 studies risk of bias for Chlorhexidine test unclear*

Figure 2 Study quality assessment using QUADAS-2 tool. Number of studies classified as low (*light grey*), unclear (*dark grey*) or high (*black*) risk of bias/concern for applicability

Figure 3 Overview of tests accuracy

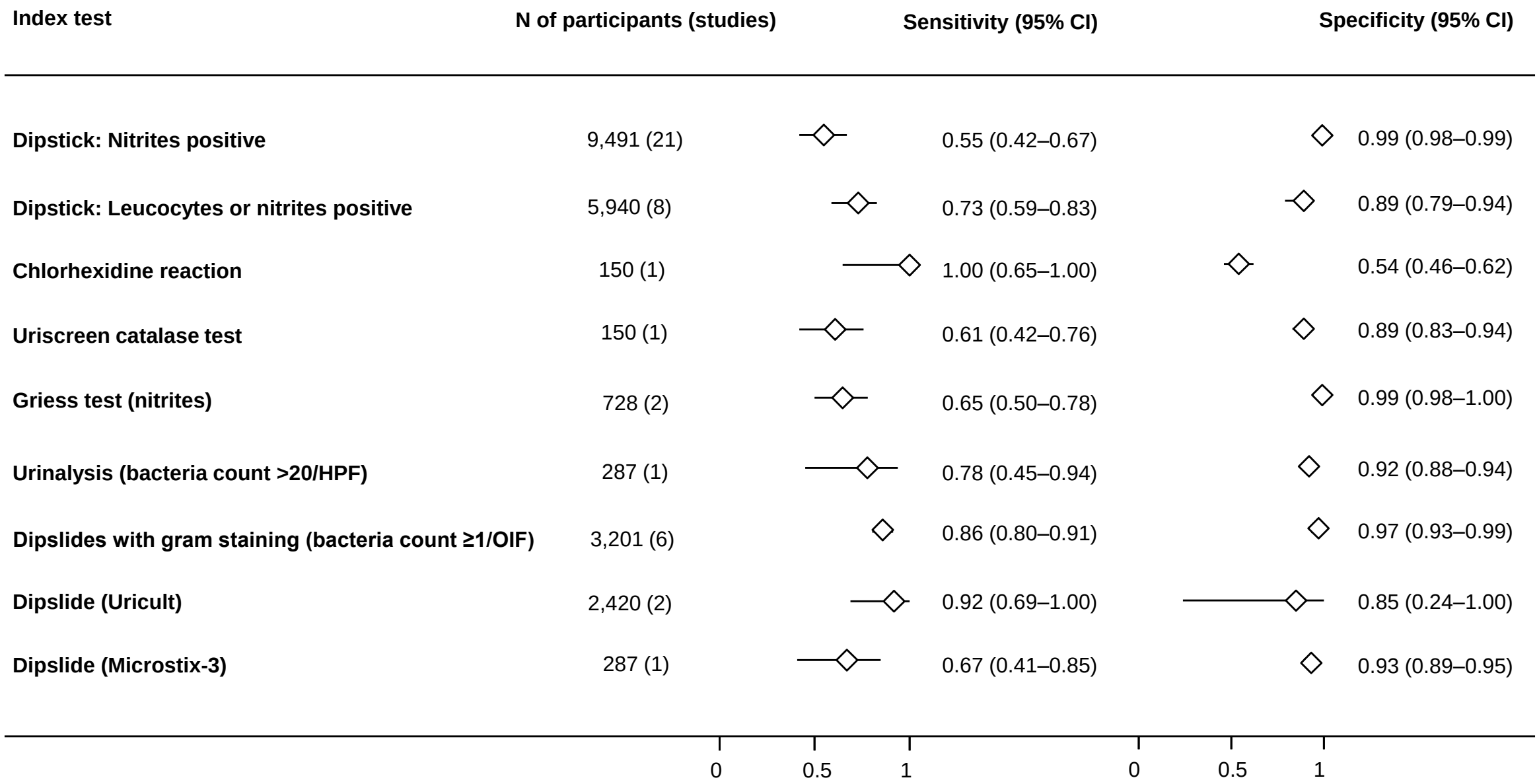


Figure 3 Overview of sensitivity and specificity of included tests to detect asymptomatic bacteriuria among pregnant women (for details see *Appendix 4*)

Appendix 1 Search strategy in MEDLINE via Ovid (19th Aug 2014 repeated on 2nd June 2015

Item	Search term
1.	Pregnancy.mp. or exp Pregnancy/
2.	exp Gravidity/
3.	gravid*.mp.
4.	gestation*.mp.
5.	exp Pregnant Women/
6.	pregnant wom#n.mp.
7.	(child adj3 bearing).mp.
8.	childbearing.mp.
9.	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10.	exp sensitivity/
11.	exp specificity/
12.	10 and 11
13.	(predictive adj3 value$).tw.
14.	(sensitivity or specificity).tw.
15.	exp Diagnostic Errors/
16.	((false adj positiv$) or (false adj negativ$)).tw.
17.	(observer adj variation$).tw.
18.	(roc adj curve).tw.
19.	(likelihood adj3 ratio$).tw.
20.	exp Likelihood Functions/
21.	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22.	exp bacteriuria/
23.	(asymptomatic$ adj2 bacteriuria$).tw.
24.	exp Urinary Tract Infections/
25.	22 or 23 or 24
26.	9 and 21 and 25

Appendix 2 Overview of test to detect asymptomatic bacteriuria reported in the retrieved literature

Group	No.	Index test	Decision	Justification for exclusion
Dipstick	1	Dipstick (marker: nitrites)	**Include**	
	2	Dipstick (marker: leucocytes or nitrites)	**Include**	
	3	Dipstick (marker: leucocytes)	Exclude	**Population:** Information not useful in asymptomatic population
	4	Dipstick (marker: leucocytes and nitrites)	Exclude	**Population:** Information not useful in asymptomatic population
Culture methods (Dip slides)	5	Uricult & Uricult Trio (Orion Diagnostica)^	**Include**	
	6	Testuria (Ayerst Labs)	Exclude	**Relevance to clinical practice:** irrelevance to current clinical practice
	7	Bacturcult (Wampole Labs)	Exclude	**Relevance to clinical practice:** irrelevance to current clinical practice
	8	Microstix-3	**Include**	
	9	Generic dipslide	Exclude	**Relevance to clinical practice:** lack of information about threshold
Microscopic techniques	10	**Microscopic analysis of urine** (marker & threshold: >20 bacteria per High Power Field	**Include**	
	11	**Dip slide with gram staining** (marker & threshold: ≥1 bacteria per oil immersed field)	**Include**	
	12	**Microscopic analysis of urine** (marker: leucocytes)	Exclude	**Population:** Not suitable to use in asymptomatic population

Group	No.	Index test	Decision	Justification for exclusion
Microscopic techniques	13	**Dip slide with gram staining** (threshold ≥2 bacteria per oil immersed field)	Exclude	**Relevance to clinical practice:** Excluded due to a threshold
Tests not usually used to detect bacteriuria	14	Uriscreen catalase tests (Savyon Diagnostics)	**Include**	
	15	Chlorhexidine reaction	**Include**	
	16	Uriglox (glucose level)	Exclude	**Relevance to clinical practice:** Test used to detect the presence or absence of the small physiological amount of glucose (2-20 mg per 100 ml)
Tests not usually used to detect bacteriuria	17	Griess test (test to detect nitrites)	**Include**	
	18	Lumac/3M Bacteriuria Screening Kit RLU>200	Exclude	**Relevance to clinical practice:** The test procedure is based upon firefly luciferase analysis of bacterial ATP. Exclude from further work as it requires lab facility
	19	Interleukin-8 5 ≥264 pg/mL	Exclude	**Relevance to clinical practice:** Interleukin-8 (IL-8), an inflammatory cytokine, is involved in host response to infection through neutrophil chemo attraction. Exclude from further work as it requires lab facility
	20	Chromogenic limulus assay	Exclude	**Relevance to clinical practice:** Not taken further due to identification of only gram negative pathogens
	21	Catalase tests	Exclude	**Data concern:** Subgroup analysis limits spectrum
	22	Triphenyl Tetrazolium Chloride	Exclude	**Data concern:** Subgroup analysis limits spectrum

Group	No.	Index test	Decision	Justification for exclusion
Automatic analysis	23	Automatic analysis of urine samples (marker & threshold: nitrites)	Exclude	**Cost:** Automated urine analysis is not widely available in resource limited settings
	24	Automatic analysis of urine samples (marker & threshold: >1200 bacteria per ml)	Exclude	**Cost:** Automated urine analysis is not widely available in resource limited settings
	25	Automatic analysis of urine samples (marker & threshold: leukocytes)	Exclude	**Population:** Information not useful in asymptomatic population
	26	Automatic analysis of urine samples (marker & threshold: leukocytes and nitrites)	Exclude	**Population:** Information not useful in asymptomatic population
	27	Automatic analysis of urine samples (Bac-T-Screen, Marion Labs)	Exclude	**Relevance to clinical practice:** Instrument is designed to provide a rapid, semi quantitative measurement of the bacteria present in urine specimens. Exclude from further work due to irrelevance to current clinical practice

Appendix 5 Reference list of all included studies

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Appendix 4 Details of urine sample collection, processing and storage in individual studies

No.	Study ID	Description of the population	Urine collection	Random voided or first morning sample	Description of urine container	Time before sending to lab	Sample storage	Sample centrifuging	Max. time of sample storage	T° Incubation of urine culture	Hours incubation of urine culture
1	Abbasi 1985	women not on antibiotics	clean catch midstream specimens	unspecified	unspecified	unspecified	unspecified	centrifuged	unspecified	unspecified	unspecified
2	Anandkumar 2011	asymptomatic women	clean catch midsteram specimens	unspecified	sterile	1 hour	unspecified	uncentrifuged	unspecified	37°C	24 hours
3	Archbald 1984	lack of detailed information	clean catch midstream specimens	random voided, at place of care	unspecified	3 hours (for IT at place), samples sent to microbiology lab for UC	unspecified	centrifuged	unspecified	unspecified	unspecified
4	Awonuga 2011	asymptomatic women	clean catch midstream specimens	unspecified	sterile	immediately	4°C	unspecified	unspecified	unspecified	unspecified
5	Bachman 1993	women not on antibiotics	clean catch midsteram specimens	random voided, at place of care	unspecified	45 minutes	unspecified	Dipstick: unspecified; Slide with gram staining: uncentrifuged	unspecified	unspecified	unspecified
6	Balamurugan 2012	asymptomatic women	clean catch midstream specimens	random voided, at place of care	sterile	1 hour	refrigerated	centrifuged	4 hours	unspecified	unspecified
7	Campos Outcalt 1985	lack of detailed information	midstream specimens	random voided, at place of care	sterile	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified
8	Demilie 2014	asymptomatic women	clean catch midstream specimens	random voided, at place of care	sterile	2 hours	4°C	unspecified	unspecified	37°C aerobically	24 hours

No.	Study ID	Description of the population	Urine collection	Random voided or first morning sample	Description of urine container	Time before sending to lab	Sample storage	Sample centrifuging	Max. time of sample storage	T° Incubation of urine culture	Hours incubation of urine culture
9	Eigbefoh 2008	asymptomatic women	clean catch midstream specimens; catheterization (8 women)	random voided, at place of care	sterile	1 hour	unspecified	uncentrifuged	unspecified	37°C	24 hours
10	Gayathree 2010	lack of detailed information	clean catch midstream specimens	unspecified	sterile	1 hour	refrigerated	uncentrifuged	unspecified	35°C aerobically	18-24 hours
11	Graninger 1992	women not on antibiotics	clean catch midstram specimems	unspecified	unspecified	30 minutes	unspecified	unspecified	unspecified	35°C	18 hours
12	Greeff 2002	asymptomatic women	midstrean specimens	random voided, at place of care	unspecified	unspecified	unspecified	uncentrifuged	unspecified	unspecified	unspecified
13	Jayalakshmi 2008	lack of detailed information	clean catch midstream specimes	unspecified	unspecified	1 hour	unspecified	uncentrifuged	unspecified	37°C aerobically	24 hours
14	Kacmaz 2006	asymptomatic women	clean catch midstream specimens	unspecified	sterile	1 hour	4°C	unspecified	4 hours	unspecified	12-24-48 hours
15	Khattak 2004	lack of detailed information	clean catch midstream specimens	random voided, at place of care	sterile	immediately	unspecified	unspecified	unspecified	37°C	unspecified
16	Kovavisarach 2008	asymptomatic women	clean catch midstrem specimes	random voided, at place of care	sterile	30 minutes	unspecified	unspecified	unspecified	35-37°C	24-48 hours
17	Mathews 1998	lack of detailed information	clean catch midstream specimens	random voided, at place of care	unspecified	immediately	unspecified	unspecified	unspecified	unspecified	unspecified

No.	Study ID	Description of the population	Urine collection	Random voided or first morning sample	Description of urine container	Time before sending to lab	Sample storage	Sample centrifuging	Max. time of sample storage	T° Incubation of urine culture	Hours incubation of urine culture
18	Mignini 2009	asymptomatic women	clean catch midstream specimens	random voided, at place of care	sterile	1 hour	4°C	unspecified	4 hours	37°C	24 hours
19	Mukherjee 2014	asymptomatic women	clean catch midstream specimens	unspecified	sterile	1 hour	4°C	uncentrifuged	24 hours	37°C aerobically	24-48 hours
20	Okusanya 2014	asymptomatic women	clean catch midstream specimens	unspecified	sterile	1 hour	4°C	Dipstick: uncentrifuged; Chlorhexidine reaction: unspecified	unspecified	unspecified	unspecified
21	Pallarés 1990	women not on antibiotics	clean catch midstream specimens	first morning	sterile	90 minutes	4°C	unspecified	unspecified	35-35°C	24 hours
22	Plauche 1981	asymptomatic women	clean catch midstream specimens	unspecified	sterile	30 minutes	unspecified	unspecified	unspecified	unspecified	unspecified
23	Shelton 2001	lack of detailed information	clean catch midstream specimens	unspecified	unspecified	immediately	unspecified	unspecified	unspecified	37°C	24 hours
24	Soisson 1985	lack of detailed information	clean catch midstream specimens	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified
25	Teppa 2005	asymptomatic women	in-and-out sterile technique of catheterization	first morning or random voided 4 hours of incubation	sterile	unspecified	4°C	unspecified	4 hours	unspecified	unspecified

No.	Study ID	Description of the population	Urine collection	Random voided or first morning sample	Description of urine container	Time before sending to lab	Sample storage	Sample centrifuging	Max. time of sample storage	T° Incubation of urine culture	Hours incubation of urine culture
26	Tincello 1998	asymptomatic women	midstream specimens	random voided, at place of care	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified	unspecified
27	Titoria 2014	asymptomatic women	clean catch midstream specimens	random voided	sterile	4 hours	unspecified	uncentrifuged	unspecified	unspecified	unspecified

Appendix 5 Overview of sensitivity and specificity reported in studies included in the review by test

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Shelton 2001	3	2	17	180	0.15 [0.03, 0.38]	0.99 [0.96, 1.00]
Kovavisarach 2008	6	3	30	321	0.17 [0.06, 0.33]	0.99 [0.97, 1.00]
Tincello 1998	9	4	39	841	0.19 [0.09, 0.33]	1.00 [0.99, 1.00]
Eigbefoh 2008	19	4	69	308	0.22 [0.14, 0.32]	0.99 [0.97, 1.00]
Demilie 2014	10	6	18	296	0.36 [0.19, 0.56]	0.98 [0.96, 0.99]
Awonuga 2011	8	3	14	180	0.36 [0.17, 0.59]	0.98 [0.95, 1.00]
Okusanya 2014	3	9	4	134	0.43 [0.10, 0.82]	0.94 [0.88, 0.97]
Soisson 1985	28	4	34	996	0.45 [0.32, 0.58]	1.00 [0.99, 1.00]
Bachman 1993	11	3	13	1020	0.46 [0.26, 0.67]	1.00 [0.99, 1.00]
Graninger 1992	68	0	58	874	0.54 [0.45, 0.63]	1.00 [1.00, 1.00]
Campos-Outcalt 1985	8	9	6	276	0.57 [0.29, 0.82]	0.97 [0.94, 0.99]
Kacmaz 2006	6	2	4	238	0.60 [0.26, 0.88]	0.99 [0.97, 1.00]
Balamurugan 2012	8	25	5	62	0.62 [0.32, 0.86]	0.71 [0.61, 0.80]
Abbasi 1985	2	0	1	62	0.67 [0.09, 0.99]	1.00 [0.94, 1.00]
Gayathree 2010	44	6	18	832	0.71 [0.58, 0.82]	0.99 [0.98, 1.00]
Mukherjee 2015	15	1	6	228	0.71 [0.48, 0.89]	1.00 [0.98, 1.00]
Jayalakshmi 2008	35	2	12	581	0.74 [0.60, 0.86]	1.00 [0.99, 1.00]
Pallares 1990	7	1	2	64	0.78 [0.40, 0.97]	0.98 [0.92, 1.00]
Titoria 2014	33	1	7	759	0.82 [0.67, 0.93]	1.00 [0.99, 1.00]
Plauche 1981	21	11	3	152	0.88 [0.68, 0.97]	0.93 [0.88, 0.97]
Archbald 1984	11	19	0	257	1.00 [0.72, 1.00]	0.93 [0.89, 0.96]

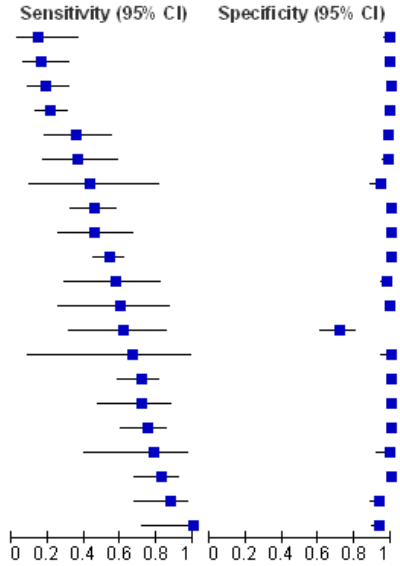

Figure 1 Overview of sensitivity and specificity in individual studies reporting use of dipstick test (only nitrites marker positive) in detecting asymptomatic bacteriuria among pregnant women

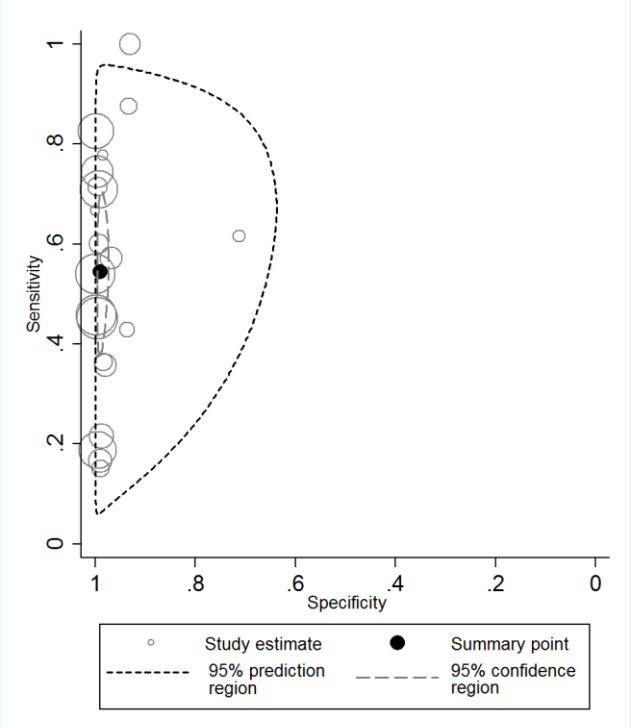

Figure 2 Receiver operating characteristic plots for studies evaluating accuracy of dipstick test (only nitrites marker positive) in detecting asymptomatic bacteriuria among pregnant women

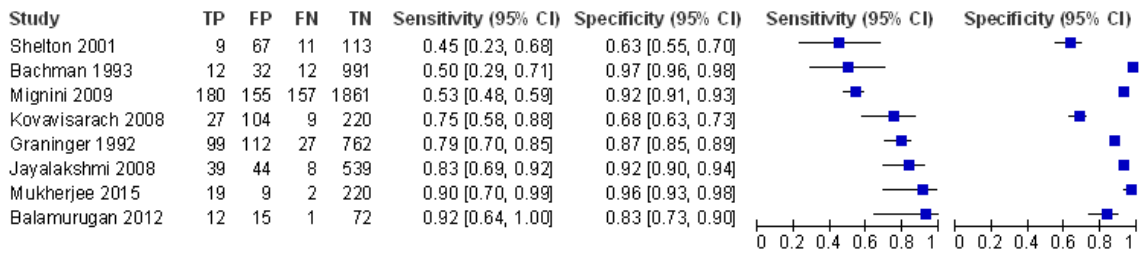

Figure 3 Overview of sensitivity and specificity in individual studies reporting use of dipstick test (nitrites or leucocytes marker positive) in detecting asymptomatic bacteriuria among pregnant women

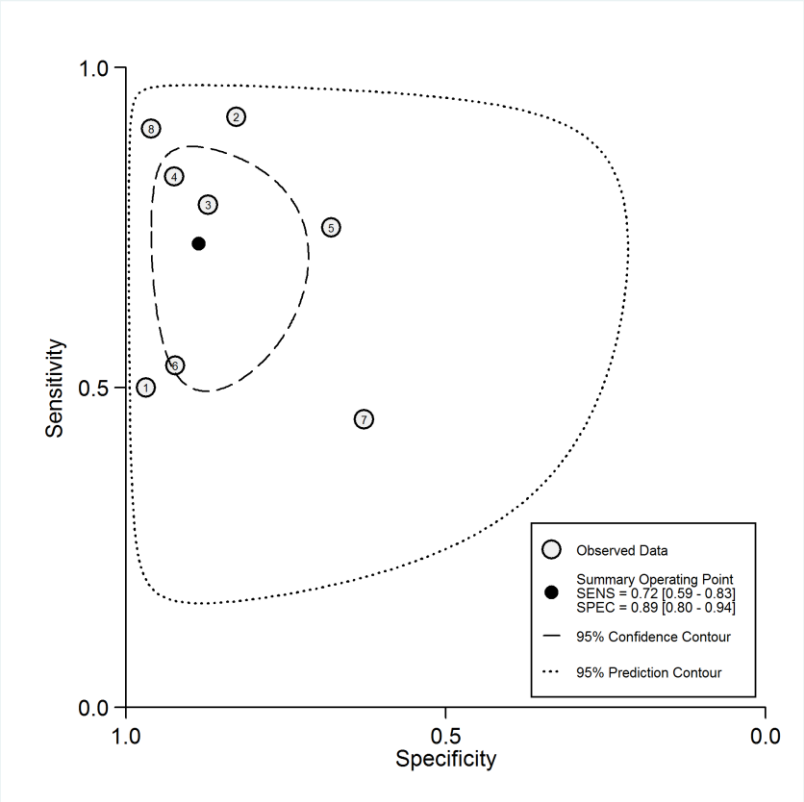

Figure 4 Receiver operating characteristic plots for studies evaluating accuracy of dipstick test (nitrites or leucocytes marker positive) in detecting asymptomatic bacteriuria among pregnant women

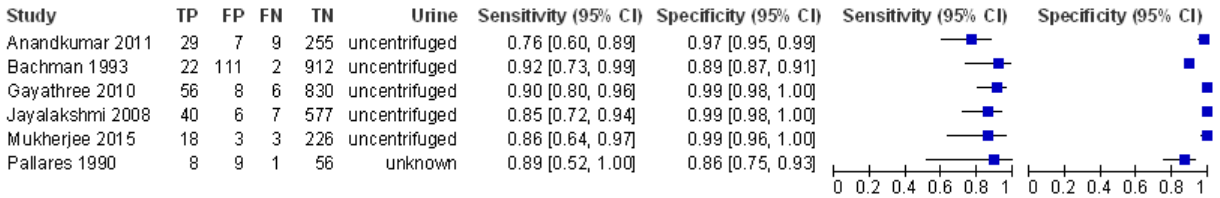

Figure 5 Overview of sensitivity and specificity in individual studies reporting use of dipslide with gram straining (more than one bacteria per OIF) in detecting asymptomatic bacteriuria among pregnant women

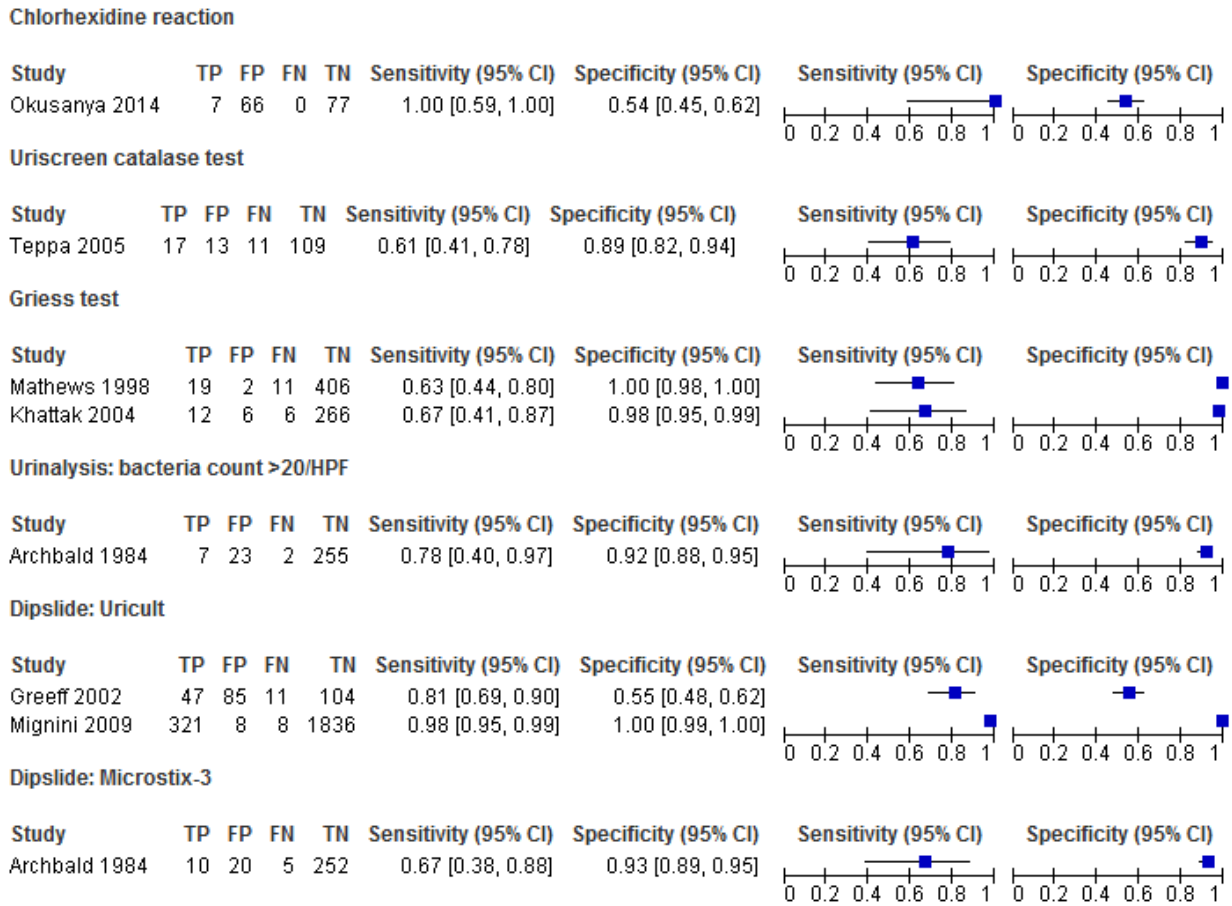

Figure 6 Overview of sensitivity and specificity in individual studies reporting use of remaining tests in detecting asymptomatic bacteriuria among pregnant women

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and

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☒ 3) Final approval of the version to be published

☒ 4) Agreement to be accountable for all aspects of the Work in ensuring that questions related to the accuracy or integrity of any part of the Work are appropriately investigated and resolved

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Supplementary materials
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	-
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Supplementary materials
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-9
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	7-8, Figure 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	10-11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11-12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097